

Tirzepatide versus insulin glargine as second-line or third-line therapy in type 2 diabetes in the Asia-Pacific region: the SURPASS-AP-Combo trial

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Supplementary Information

Supplementary Table 1: HbA1c values over time

HbA1c (%) (LSMean)		Efficacy Analysis Set				Per-Protocol Analysis Set			
		TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin glargine	TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin glargine
Baseline	n	228	222	224	215	206	185	190	197
		8.77	8.70	8.67	8.68	8.77	8.74	8.64	8.69
Week 4	n	218	217	215	203	197	180	181	185
		7.76	7.74	7.77	8.34	7.77	7.73	7.78	8.36
Week 8	n	216	212	212	204	199	183	185	191
		6.93	6.91	6.97	7.92	6.93	6.90	6.99	7.94
Week 12	n	214	207	201	203	199	184	182	190
		6.52	6.41	6.43	7.66	6.52	6.39	6.46	7.69
Week 16	n	212	197	193	202	200	181	180	190
		6.36	6.17	6.16	7.52	6.35	6.13	6.19	7.54
Week 20	n	213	196	196	200	203	183	184	193
		6.35	6.10	6.06	7.50	6.34	6.06	6.08	7.51
Week 24	n	205	190	188	192	197	180	179	186
		6.39	6.10	6.08	7.49	6.39	6.05	6.10	7.50
Week 40	n	211	194	193	193	205	185	190	189
		6.47	6.27	6.22	7.76	6.46	6.24	6.23	7.77

HbA1c, glycated hemoglobin; LSMean, least-squares mean; n, number of patients with baseline and post-baseline value at the specified time point; TZP, tirzepatide.

Supplementary Table 2: Bodyweight values over time

Body weight (kg) (LSMean)		Efficacy Analysis Set				Per-Protocol Analysis Set			
		TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin glargine	TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin glargine
Baseline	n	228	222	224	215	206	185	190	197
		77.8	76.5	76.3	75.5	77.7	77.1	77.6	75.2
Week 4	n	219	218	216	204	198	181	182	186
		75.5	75.4	75.4	76.7	75.6	75.6	75.6	76.7
Week 8	n	220	212	212	206	202	183	185	192
		74.1	74.0	74.0	77.1	74.2	74.1	74.1	77.1
Week 12	n	216	208	203	204	200	184	184	191
		73.4	72.8	72.8	77.4	73.6	73.0	73.0	77.3
Week 16	n	213	197	195	203	201	181	182	191
		73.0	71.8	71.9	77.7	73.2	71.9	72.1	77.7
Week 20	n	214	196	197	203	204	183	185	195
		72.5	71.1	70.9	78.0	72.7	71.3	71.1	78.0
Week 24	n	208	190	188	194	200	180	179	188
		72.2	70.5	70.2	78.0	72.4	70.7	70.4	77.9
Week 32	n	201	188	187	184	194	179	181	179
		72.1	70.2	70.0	78.6	72.4	70.4	70.2	78.6
Week 40	n	211	194	193	194	205	185	190	189
		71.7	69.7	69.5	78.2	71.9	69.8	69.7	78.2

LSMean, least-squares mean; n, number of patients with baseline and post-baseline value at the specified time point; TZP, tirzepatide.

Supplementary Table 3: Summary of mean DTSQs Scores at Baseline and DTSQc Scores at Week 40

Scale score/ time point	Tirzepatide 5 mg (N=230)	Tirzepatide 10 mg (N=228)	Tirzepatide 15 mg (N=229)	Insulin glargine (N=220)
Total^a				
n	212	200	195	196
DTSQs at baseline	29.4	29.5	30.1	29.4
DTSQc at Week 40 (LOCF)	16.0	15.8	15.9	14.2
Difference from insulin glargine in DTSQc (95% CI)	1.81*** (1.03, 2.59)	1.63*** (0.84, 2.41)	1.68*** (0.89, 2.47)	NA

DTSQs scores were collected at baseline visit. DTSQc scores were collected at Week 40 or an early termination visit if the patient was unable or unwilling to continue the study. Data are shown as least-squares means. DTSQs was estimated using an ANOVA and DTSQc was estimated using an ANCOVA without missing-value imputation in the in patients, all statistical tests were two sided at a significance level of 0.05. The last available postbaseline observation was applied to impute the endpoint.

^aA greater score indicates greater patient satisfaction with treatment.

***p-value <0.001 versus insulin glargine.

ANCOVA, analysis of covariance; ANOVA, analysis of variance; CI, confidence interval; DTSQc, Diabetes Treatment Satisfaction Questionnaire (Change); DTSQs, Diabetes Treatment Satisfaction Questionnaire (Status); LOCF, last observation carried forward; N, number of patients who were randomized and received at least 1 dose of study drug; n, number of patients with baseline and post-baseline value at the specified time point; NA, not applicable.

Supplementary Table 4: Serious adverse events (safety analysis set)

Serious adverse events, n (%)	Tirzepatide 5 mg (N=230)	Tirzepatide 10 mg (N=228)	Tirzepatide 15 mg (N=229)	Insulin glargine (N=220)
≥1 serious adverse event	15 (6.5)	14 (6.1)	15 (6.6)	20 (9.1)
Nervous system disorders	4 (1.7)	1 (0.4)	5 (2.2)	2 (0.9)
Cerebral infarction	3 (1.3)	0 (0)	2 (0.9)	1 (0.5)
Vertebrobasilar insufficiency	0 (0)	0 (0)	2 (0.9)	1 (0.5)
Cerebellar hemorrhage	0 (0)	1 (0.4)	0 (0)	0 (0)
Cerebral ischaemia	0 (0)	0 (0)	1 (0.4)	0 (0)
Lacunar infarction	1 (0.4)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	4 (1.7)	5 (2.2)	0 (0)	1 (0.5)
Inguinal hernia	1 (0.4)	1 (0.4)	0 (0)	0 (0)
Anal fissure	0 (0)	1 (0.4)	0 (0)	0 (0)
Colitis	1 (0.4)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	1 (0.4)	0 (0)	0 (0)
Gastritis	1 (0.4)	0 (0)	0 (0)	0 (0)
Gastrointestinal hemorrhage	1 (0.4)	0 (0)	0 (0)	0 (0)
Mechanical ileus	0 (0)	1 (0.4)	0 (0)	0 (0)
Pancreatitis acute	0 (0)	0 (0)	0 (0)	1 (0.5)
Umbilical hernia	0 (0)	1 (0.4)	0 (0)	0 (0)
Infections and infestations	1 (0.4)	1 (0.4)	2 (0.9)	4 (1.8)
Appendicitis	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Epididymitis ^a	0 (0)	0 (0)	0 (0)	1 (0.8)
Febrile infection	0 (0)	0 (0)	0 (0)	1 (0.5)
Gastroenteritis	0 (0)	0 (0)	1 (0.4)	0 (0)
Herpes zoster	1 (0.4)	0 (0)	0 (0)	0 (0)
Pneumonia	0 (0)	0 (0)	0 (0)	1 (0.5)
Urinary tract infection	0 (0)	0 (0)	0 (0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9)	3 (1.3)	2 (0.9)	1 (0.5)
Papillary thyroid cancer	1 (0.4)	2 (0.9)	0 (0)	0 (0)
Adenocarcinoma of colon	0 (0)	0 (0)	0 (0)	1 (0.5)
Benign breast neoplasm	0 (0)	0 (0)	1 (0.4)	0 (0)
Breast cancer	0 (0)	0 (0)	1 (0.4)	0 (0)
Lipoma	0 (0)	1 (0.4)	0 (0)	0 (0)
Meningioma	1 (0.4)	0 (0)	0 (0)	0 (0)
Ovarian germ cell teratoma ^b	0 (0)	0 (0)	1 (1)	0 (0)
Injury, poisoning and procedural complications	0 (0)	2 (0.9)	0 (0)	4 (1.8)
Meniscus injury	0 (0)	1 (0.4)	0 (0)	1 (0.5)
Femur fracture	0 (0)	0 (0)	0 (0)	1 (0.5)
Muscle rupture	0 (0)	1 (0.4)	0 (0)	0 (0)
Road traffic accident	0 (0)	0 (0)	0 (0)	1 (0.5)
Wrist fracture	0 (0)	0 (0)	0 (0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0 (0)	2 (0.9)	1 (0.4)	2 (0.9)
Osteoarthritis	0 (0)	1 (0.4)	0 (0)	1 (0.5)
Intervertebral disc protrusion	0 (0)	1 (0.4)	0 (0)	0 (0)
Spinal osteoarthritis	0 (0)	0 (0)	1 (0.4)	0 (0)
Spondylolisthesis	0 (0)	0 (0)	0 (0)	1 (0.5)
Cardiac disorders	1 (0.4)	0 (0)	1 (0.4)	2 (0.9)
Atrial fibrillation	0 (0)	0 (0)	0 (0)	1 (0.5)
Cardiac failure acute	1 (0.4)	0 (0)	0 (0)	0 (0)
Coronary artery disease	0 (0)	0 (0)	0 (0)	1 (0.5)
Myocardial infarction	0 (0)	0 (0)	1 (0.4)	0 (0)

Ear and labyrinth disorders	0 (0)	0 (0)	1 (0.4)	2 (0.9)
Vertigo	0 (0)	0 (0)	1 (0.4)	2 (0.9)
Hepatobiliary disorders	1 (0.4)	1 (0.4)	1 (0.4)	0 (0)
Cholecystitis acute	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Cholelithiasis	1 (0.4)	0 (0)	0 (0)	0 (0)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0 (0)	0 (0)	0 (0)
Ectopic pregnancy ^b	1 (1)	0 (0)	0 (0)	0 (0)
Reproductive system and breast disorders	0 (0)	0 (0)	1 (0.4)	1 (0.5)
Adenomyosis ^b	0 (0)	0 (0)	0 (0)	1 (1)
Perineal pain	0 (0)	0 (0)	1 (0.4)	0 (0)
Eye disorders	0 (0)	0 (0)	1 (0.4)	1 (0.5)
Cataract	0 (0)	0 (0)	0 (0)	1 (0.5)
Macular oedema	0 (0)	0 (0)	1 (0.4)	0 (0)
General disorders and administration site conditions	0 (0)	0 (0)	1 (0.4)	1 (0.5)
Sudden cardiac death	0 (0)	0 (0)	0 (0)	1 (0.5)
Sudden death	0 (0)	0 (0)	1 (0.4)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.4)	0 (0)	1 (0.5)
Nasal polyps	0 (0)	1 (0.4)	0 (0)	0 (0)
Vocal cord polyp	0 (0)	0 (0)	0 (0)	1 (0.5)
Blood and lymphatic system disorders	1 (0.4)	0 (0)	0 (0)	0 (0)
Lymphoid tissue hyperplasia	1 (0.4)	0 (0)	0 (0)	0 (0)
Investigations	0 (0)	0 (0)	0 (0)	1 (0.5)
Cardiac function test	0 (0)	0 (0)	0 (0)	1 (0.5)
Renal and urinary disorders	0 (0)	1 (0.4)	0 (0)	0 (0)
Calculus urinary	0 (0)	1 (0.4)	0 (0)	0 (0)

^aDenominator adjusted because gender-specific event for males: n=134 (tirzepatide 5 mg), n=126 (tirzepatide 10 mg), n=129 (tirzepatide 15 mg), n=118 (insulin glargine);

^bDenominator adjusted because gender-specific event for females: n=96 (tirzepatide 5 mg), n=102 (tirzepatide 10 mg), n=100 (tirzepatide 15 mg), n=102 (insulin glargine).

N, number of patients who were randomized and received at least 1 dose of study drug; n, number of patients with events meeting specified criteria.

Supplementary Table 5: Duration of Diarrhea, Nausea and Vomiting

Median, days	Tirzepatide 5 mg (N=230)	Tirzepatide 10 mg (N=228)	Tirzepatide 15 mg (N=229)	Insulin glargine (N=220)
Diarrhea	3	3	3	2
Nausea	3	3	4	8.5
Vomiting	1	2	2	1.5

N, number of patients who were randomized and received at least 1 dose of study drug.

Supplementary Table 6: Changes in SBP, DBP and pulse rate from Baseline to Week 40

	Tirzepatide 5 mg (N=230)	Tirzepatide 10 mg (N=228)	Tirzepatide 15 mg (N=229)	Insulin glargine (N=220)
Pulse (bpm)				
Baseline	77.9	77.3	77.9	78.4
Change from baseline	2.2 ^{†††}	4.2 ^{†††}	4.8 ^{†††}	0.7
Change difference from insulin glargine (95% CI)	1.5 [†] (-0.2, 3.2)	3.5 ^{***} (1.8, 5.2)	4.1 ^{***} (2.4, 5.8)	N/A
SBP (mm Hg)				
Baseline	129.5	129.3	129.0	128.0
Change from baseline	-6.7 ^{†††}	-7.2 ^{†††}	-7.3 ^{†††}	1.1
Change difference from insulin glargine (95% CI)	-7.8 ^{***} (-10.0, -5.6)	-8.3 ^{***} (-10.6, -6.1)	-8.4 ^{***} (-10.6, -6.2)	N/A
DBP (mm Hg)				
Baseline	83.4	83.0	82.0	82.7
Change from baseline	-4.0 ^{†††}	-3.6 ^{†††}	-3.4 ^{†††}	0.9
Change difference from insulin glargine (95% CI)	-3.2 ^{***} (-4.6, -1.7)	-2.8 ^{***} (-4.2, -1.3)	-2.5 ^{***} (-3.9, -1.1)	N/A

Data are shown as least-squares means which were estimated using an MMRM without missing-value imputation in the in patients who received at least 1 dose of study drug. Only patients with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in the analysis.

†††p-Value <0.001 versus baseline.

***p-value <0.001 versus insulin glargine.

[†]p-value=0.081 versus insulin glargine.

bpm, beats per minute; CI, confidence interval; DBP, diastolic blood pressure; MMRM, mixed model for repeated measures; N, number of patients who were randomized and received at least 1 dose of study drug; N/A, not applicable; SBP, systolic blood pressure.

Supplementary Table 7: Summary of lipid-lowering medication use at baseline and post-baseline

	Tirzepatide 5 mg (N=230)	Tirzepatide 10 mg (N=228)	Tirzepatide 15 mg (N=229)	Insulin glargine (N=220)	Overall p-value*
Patients with ≥ 1 lipid-lowering therapy, n (%)					
Baseline	60 (26.1)	68 (29.8)	67 (29.3)	60 (27.3)	0.796
Post-baseline	66 (28.7)	71 (31.1)	76 (33.2)	71 (32.3)	0.750

* P value for overall treatment effect was computed using Fisher's exact test.

N, number of patients who were randomized and received at least 1 dose of study drug; n, number of patients in the specific category.

Supplementary Table 8: Changes in UACR

	Tirzepatide 5 mg (N=230)	Tirzepatide 10 mg (N=228)	Tirzepatide 15 mg (N=229)	Insulin glargine (N=220)
Baseline, g/kg	27.0	24.0	23.6	20.5
Change from baseline, g/kg (%)	-8.8 (-37.3)	-11.5 (-48.5)	-10.0 (-42.1)	-2.3 (-9.8)
Insulin glargine adjusted change difference, % (95% CI)	-30.5*** (-41.0, -18.2)	-43.0*** (-51.6, -32.8)	-35.8*** (-45.5, -24.4)	N/A

Data shown as estimated means which were estimated using an ANCOVA without missing-value imputation in the in patients who received at least 1 dose of study drug, all statistical tests were two sided at a significance level of 0.05. Only patients with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in analysis.

***p-value <0.001 versus insulin glargine.

ANCOVA, analysis of covariance; CI, confidence interval; N, number of patients who were randomized and received at least 1 dose of study drug; N/A, not applicable; UACR, urine albumin to creatinine ratio.

Supplementary Table 9: List of ethics review boards

Investigator Name/ Site Number	Ethics Review Board's Name and Address
P.R.China	
Song Lu/100	Ethics Committee of Chongqing General Hospital. No.104, PipaShan Street, Yuzhong District, Chongqing, 400013, P.R.China
Li Nong Ji/101	Ethics Committee of Peiking University People's Hospital No.11, Xizhimen South Street, Xicheng District, Beijing, 100044, P.R.China
Yuxiu Li/102	Ethics Committee of Drug Clinical Trials of Peking Union Medical College Hospital No.1, Shuaifuyuan, Dongcheng District, Beijing, 100730, P.R.China
Ming Liu/103	Ethics Committee of Drug Clinical Trials, General Hospital of Tianjin Medical University No.154, Anshan Road, Heping District, Tianjin, 300052, P.R.China
Tao Lei/104	Ethics Committee of Shanghai Putuo District Central Hospital No.164, Lanxi Road, Putuo District, Shanghai, 200333, P.R.China
Fang Bian/106	Drug Clinical Trial Ethics Committee of Cangzhou People's Hospital No.7, Qingchi Avenue, Xinhua District, Cangzhou, Hebei, 061000, P.R.China
Tao Ning/109	Ethics Committee of Baotou Central Hospital No.81, Huancheng Road, Donghe District, Baotou City, Mongolia Autonomous Region, 104040, P.R.China
Lian Guo/110	Drug clinical trials Ethics Committee of Chongqing University Three Gorges Hospital No.165, Xincheng Road, Wanzhou District, Chongqing, 404000, P.R.China
Wenhui Zhao/112	Ethics Committee of Beijing Tsinghua Changgung Hospital No.168, Litang Road, Changping District, Beijing, 102218, P.R.China
Wei Duan/113	Ethics Committee of Drug Clinical Trials, Affiliated Zhongshan Hospital of Dalian University No.6, Jiefang Street, Zhongshan District, Dalian City, Liaoning Province, 116001, P.R.China
Kun Wang/115	Nanjing Jiangning Hospital Ethics Committee Nanjing Jiangning Hospital, No. 169, Hushan Road, Jiangning District, Nanjing, 211199, P.R.China
Hongyi Cao/116	Ethics Committee of the Fifth People's Hospital of Chengdu No.33, Mashi Street, Wenjiang District, Chengdu City, Sichuan Province, P.R.China
Yufeng Li/117	Ethics Committee of Beijing Pinggu Hospital No.59, Xinping North Road, Pinggu District, Beijing, 101200, P.R.China
Zhifeng Cheng/118	Clinical Trial Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University No.37, Yiyuan Street, Nangang District,

	Harbin, Heilongjiang Province, 150001, P.R.China
Bimin Shi/119	Medical Ethics Committee of The First Affiliated Hospital of Soochow University No.899, Pinghai Road, Suzhou, Jiangsu Province, 215031, P.R.China
Guoyue Yuan/120	Ethics Committee of Affiliated Hospital of Jiangsu University No.438, Jiefang Road, Zhenjiang, Jiangsu Province, 212001, P.R.China
Lei Chen/121	Ethics Committee of Suzhou Municipal Hospital No.26, Daoqian Street, Suzhou, Jiangsu Province, 215006, P.R.China
Xiaoyue Wang/122	Ethics Committee of Yueyang Central Hospital No.28, Yueyang Dadao, Yueyang Lou District, Yueyang City, Hunan Province, 414000, P.R.China
Yun Xue/123	Ethics Committee of Changzhou No.2 People's Hospital No.29, Xinglong Lane, Tianning District, Changzhou City, Jiangsu Province, 213003, P.R.China
Tianshu Zeng/124	Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology No.13, Hangkong Road, Wuhan, Hubei Province, China
Xiaolin Dong/125	Jinan Central Hospital Medical Ethics Committee, No.105, Jiefang Road, Lixia District, Jinan City, 250014, P.R.China
Yawei Zhang/126	Ethics Committee of Pingxiang People's Hospital No.8, Wugongshan Avenue, Pingxiang City, Jiangxi Province, 337055, P.R.China
Peng Duan/129	Ethics Committee of Nanchang Third Hospital No.2, Xiangshan South Road, Nanchang City, 330000, P.R.China
Yujin Ma/130	Medical Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology No.24, Jinghua Road, Jianxi District, Luoyang, Henan, 471000, P.R.China
Jing Yang/131	Ethics Committee of First Hospital of Shanxi Medical University No.85, South Jiefang Road, Yingze District, Taiyuan City, Shanxi Province, 030001, P.R.China
Qingju Li/133	Clinical Trial Ethics Committee of the Second Affiliated Hospital of Zhengzhou University, No.2, Jingba Road, Jinshui District, Zhengzhou City, Henan Province, 450000, P.R.China
Yan Bi/134	Medical Ethics Committee of The affiliated Hospital of Nanjing University Medical School No.321, Zhongshan Road, Gulou District, Nanjing, 210000, P.R.China
Jianhua Ma/135	Ethics Committee of Nanjing First Hospital No.68, Changle Road, Qinhuai District, Nanjing City, Jiangsu Province, 210029, P.R.China
Shu Li/136	Ethics Committee of Huizhou Central People's Hospital No.41, Eling North Road, Huizhou City, Guangdong Province, 516001, P.R.China
Jingna Lin/137	Ethics Committee of Tianjin People's Hospital No.190, Jieryuan Road, Hongqiao District, Tianjin, 300000, P.R.China

Jianping Yao/138	Ethics Committee of Huzhou central hospital No.1558, Sanhuan North Road, Wuxing District, Huzhou City, P.R.China
Bingyin Shi/139	Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University No.277, Yanta West Road, Xi'an City, Shanxi Province, P.R.China
Ya Li/140	Medical Ethics Committee of the First Affiliated Hospital of Xi'an Medical University No.48, Fenghao West Road, Lianhu District, Xi 'an City, Shanxi Province, 710077, P.R.China
Yibing Lu/141	Ethics Committee of The Second Affiliated Hospital of Nanjing Medical University No.121 Jiangjiayuan, Jiangjiayuan Road, Gulou District, Nanjing City, Jiangsu Province, P.R.China
Minxiu Yao/142	Qingdao Central Hospital Medical Ethics Committee No.127, Siliu South Road, Shibei District, Qingdao, 266000, P.R.China
Yan Ren/143	Ethics Review Committee of Clinical Trials, West China Hospital, Sichuan University No.37, Guoxue Lane, Wuhou District, Chengdu City, Sichuan Province, P.R.China
Chunying Deng/144	Ethics Committee of the Fourth People's Hospital of Zigong City No.19, Tanmulin Street, Ziliujing District, Zigong City, Sichuan Province, P.R.China
Xuwei Si/145	Academic Ethics Committee of Shaoxing People's Hospital No.568, Zhongxing North Road, Shaoxing City, Zhejiang Province, 312000, P.R.China
Bing He/146	The Medical Ethics Committee of Shengjing Hospital Affiliated to China Medical University, No.36, Sanhao Street, Heping District, Shenyang City, Liaoning Province, 110000, P.R.China
Zunhai Zhou/148	Ethics Committee of Shanghai Yangpu District Central Hospital No.450, Tengyue Road, Shanghai, P.R.China
Shan Huang/149	Ethics Committee of Shanghai Tongren Hospital No.419, Hami Road, Shanghai, P.R.China
Lan Xu/150	Ethics Committee of Wuxi People's Hospital No.299, Qingyang Road, Liangxi District, Wuxi City, Jiangsu Province, P.R.China
Li Ling/152	Clinical Research Ethics Committee of Zhongda Hospital Southeast University No.87, Dingjiaqiao, Gulou District, Nanjing City, Jiangsu Province, 210009, P.R.China
Yuqian Bao/153	Shanghai 6th People's Hospital No.600, Yishan Road, Xuhui District, Shanghai, P.R.China
Gui Xia Wang/154	Ethics Committee of the First Hospital of Jilin University No.1, Xinmin Street, Changchun City, Jilin Province, 130000, P.R.China

Jian Lin Geng/155	Ethics Committee of Hebei Medical University (Harrison International Peace Hospital) No.180, East Renmin Road, Taocheng District, Hengshui City, Hebei Province, 053000, China
Republic of Korea	
Jae Myung Yu/200	Hallym University Kangnam Sacred Heart Hospital 1, Singil-ro, Yeongdeungpo-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea
Soon-Jib Yoo/201	Bucheon St. Marys Hospital 327, Sosa-ro, Bucheon-si, Gyeonggi-do, Republic of Korea
Choon Hee Chung/202	Yonsei University-Wonju Severance Christian Hospital 20 Ilsan-ro, Wonju, Kangwon-do, Republic of Korea
EunSook Kim/203	Ulsan University Hospital 877 Bangeojinsunhwan-doro, Dong-gu, Ulsan, Ulsan-Kwangyöksi, Republic of Korea
Hye Soon Kim/204	Keimyung University Dongsan Hospital 1035, dalgubeol-daero, Dalseo-gu, Daegu, Taegu-Kwangyöksi, Republic of Korea
Sin Gon Kim/205	Korea University Anam Hospital 73, Goryedae-ro, Seongbuk-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea
Kyu Jeung Ahn/206	Kyung Hee University Hospital at Gangdong 892 Dongnam-ro, Gangdong-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea
Chang Beom Lee/207	Hanyang University Guri Hospital 153, Gyeongchun-ro, Guri-si, Gyeonggi-do, Republic of Korea
Nan Hee Kim/208	Korea University Ansan Hospital 123, Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Republic of Korea
Byung Wan Lee/209	Severance Hospital, Yonsei University Health System 50-1 Yonsei-ro, Seodaemun-gu Seoul, Seoul-teukbyeolsi, Republic of Korea
Woo Je Lee/210	Asan Medical Center 2F, Clinical Research Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea
Jong Chul Won/212	Inje University Sanggye Paik Hospital 1342 Dongil-ro, Nowon-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea
Soo Lim/214	Seoul National University Bundang Hospital, ERB Department, 82 Gumi-ro 173 beon-gil, Bundang-Gu, Seongnam, Gyeonggi-do, Republic of Korea
Australia	
Shannon McCarthy/300	Monash Health 246 Clayton Road, Clayton, Victoria, 3168, Australia
Christopher Argent/301 (2019-2020) Joshua Kim/301 (2020-2022)	Monash Health 246 Clayton Road, Clayton, Victoria, 3168, Australia
James Vandeleur/302 (2019) Joshua Kim/302 (2019-2022)	Monash Health 246 Clayton Road, Clayton, Victoria, 3168, Australia

Mark Bloch/303	Monash Health 246 Clayton Road, Clayton, Victoria, 3168, Australia
Sepehr Shakib/304 (2019-2022) Emir Redzepagic/304 (2021-2021)	Monash Health 246 Clayton Road, Clayton, Victoria, 3168, Australia
Robert Moses/305 (2019-2020) Alexia Pape/305 (2021-2022)	Monash Health 246 Clayton Road, Clayton, Victoria, 3168, Australia
India	
Ajay Aggarwal/400	Institutional Ethics Committee Fortis Hospital, A block, Shalimar Bagh, Delhi 110088 India
Manoj Satesh Chawla/401	BSES Municipal General Hospital Ethics Committee, Mumbai S. V. Road, Opp. Railway Station, Andheri (W), Mumbai, Maharashtra 400058 India
Jagat Jyoti Mukherjee/402	Institutional Ethics Committee Apollo Gleneagles Hospital, Kolkata 58, Canal Circular Road, Kolkata, West Bengal 700054 India
Tushar Ramkrishna Bandgar/403	Institutional Ethics Committee-I Seth GS Medical College & KEM Hospital Acharya Donde Marg, Parel, Mumbai – 400012 India

Supplementary Table 10: Insulin glargine dose titration algorithm

Average of self-monitored plasma-equivalent FBG measurements from the previous 2-4 days	Change in insulin glargine dose (IU/day)
≥6.1 mmol/L (≥110 mg/dL)	+2
5.6 – 6.1 mmol/L (101 – 109 mg/dL)	+1 or +2 (at the investigator's discretion)
4.0 – 5.6 mmol/L (72 – 100 mg/dL)	No change in dosage
3.3 – 3.9 mmol/L (60 – 71 mg/dL)	-1
<3.3 mmol/L (<60 mg/dL)	-2

Notes: The FBG concentrations listed above refer to fasting plasma glucose concentrations obtained from a laboratory or FBG concentrations obtained using an International Federation of Clinical Chemistry (IFCC) plasma-equivalent BG meter. If only one prebreakfast SMBG value is available, the patient should contact the investigator site for instructions on adjusting insulin dose.

BG, blood glucose; FBG, fasting blood glucose; SMBG, self-monitored blood glucose.

Source: Kawamori et al. *Diabetes Res Clin Pract*. 2008. DOI: 10.1016/j.diabres.2007.08.007

Criteria for severe, persistent hyperglycemia

- (a) Average daily BG from the once-weekly 4-point SMBG profile >15.0 mmol/L (>270 mg/dL) over at least a consecutive 2-week period any time during the first 8 weeks post randomization;

OR

- (b) Average daily BG from the once-weekly 4-point SMBG profile >13.3 mmol/L (>240 mg/dL) over a consecutive 2-week period at any time 9 to 16 weeks post randomization;

OR

- (c) Average daily BG from the once-weekly 4-point SMBG profile >11.1 mmol/L (>200 mg/dL) over a consecutive 2-week period at any time beyond the first 16 weeks post randomization;

OR

- (d) HbA1c $\geq 8.5\%$ at 24 weeks, with inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months (week 12 to week 24) that is $< 0.3\%$.

Complete list of eligibility criteria

Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria at screening:

Type of Patient and Disease Characteristics

- [1] Have been diagnosed with type 2 diabetes based on the WHO classification or other locally applicable diagnostic standards

Patient Characteristics

- [2] Are on stable diabetes treatment with metformin with or without a Sulfonylurea (metformin ≥ 1000 mg/day and no more than the maximum approved dose per country-specific label; sulfonylurea should be at least half the maximum dose according to the specific country label information) for at least 2 months prior to Visit 1 and between Visit 1 and Visit 3.
- [3] Are insulin-naïve (except for the use of insulin for treatment of gestational diabetes or short-term use [≤ 14 consecutive days] for acute conditions)

- [4] Have HbA1c $\geq 7.5\%$ to $\leq 11.0\%$, as determined by the central laboratory at Visit 1
- [5] Are of stable weight ($\pm 5\%$) ≥ 3 months prior to Visit 1, and agree to not initiate a diet and/or exercise program during the study with the intent of reducing bodyweight other than the lifestyle and dietary measures for diabetes treatment
- [6] Have body mass index (BMI) $\geq 23 \text{ kg/m}^2$ at Visit 1
- [7] Are ≥ 18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older

Male patients:

- Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection

Female patients:

- Female patients not of childbearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation), congenital anomaly (ie. Mullerian agenesis) or menopause.
 - Women with an intact uterus are deemed postmenopausal if they are 45 years old, and have not taken hormones or oral contraceptives within the last year and had cessation of menses for at least 1 year,

OR

- have had at least 6 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH $\geq 40 \text{ mIU/mL}$ and estradiol $< 30 \text{ pg/mL}$).
- Female patients of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:
 - test negative for pregnancy at Visit 1 based on a serum pregnancy test

AND

- if sexually active, agree to use two forms of effective contraception, where at least one form is highly effective for the duration of the trial and for 30 days thereafter
 - not be breastfeeding
- [8] In the investigator's opinion, are well-motivated, capable, and willing to:
- a) perform fingerstick BG monitoring, including scheduled BG profiles with up to 7 measurements in 1 day
 - b) learn how to self-inject treatment (tirzepatide or insulin glargine), as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the

study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)

c) are willing and able to inject tirzepatide once-weekly or insulin glargine QD

d) maintain a study diary, as required for this protocol.

e) have a sufficient understanding of the primary language of the country such that they will be able to complete the patient questionnaires

Informed Consent

- [9] Have given written informed consent to participate in this study in accordance with local regulations and the Ethical Review Board (ERB) governing the study site

Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

- [10] Have Type 1 diabetes mellitus (T1DM)

- [11] Had chronic or acute pancreatitis any time prior to study entry (Visit 1).

- [12] Have history of:

- proliferative diabetic retinopathy

or

- diabetic maculopathy

or

- nonproliferative diabetic retinopathy that requires acute treatment

(a dilated fundoscopic examination will be performed for all patients between Visit 2 and Visit 3, unless there is a contraindication to dilate the eye [ie. closed angle glaucoma]. The diagnosis will be made by an eye care professional [ophthalmologist or optometrist] before Visit 3 to confirm eligibility)

- [13] Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1

- [14] Have a history of ketoacidosis or hyperosmolar state/coma

- [15] Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone or plan to have during the course of the study: a gastric bypass (bariatric) surgery, or restrictive bariatric surgery (eg, Lap-Band®), or chronically take drugs that directly affect GI motility

- [16] Have any of the following CV conditions within 2 months prior to Visit 1: acute myocardial infarction, or cerebrovascular accident (stroke) or hospitalization due to congestive heart failure (CHF)
- [17] New York Heart Association Functional Classification III and IV CHF
- [18] Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >3.0 times the upper limit of the reference range, as determined by the central laboratory at study entry (visit 1); patients with NAFLD are eligible for participation in this trial only if their ALT level is ≤3.0 times the upper limit of normal (ULN) for the reference range
- [19] Have an estimated glomerular filtration rate (eGFR) ≤45 mL/min/1.73 m² (or lower than the country-specific threshold for using the protocol-required dose of metformin per local label), calculated by CKD-EPI, as determined by central laboratory at Visit 1
- [20] Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis or adrenal crises), in the opinion of the investigator
- [21] Have family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN-2)
- [22] Have a serum calcitonin level of ≥35 ng/L (pg/mL), as determined by central laboratory at Visit 1
- [23] Known or suspected hypersensitivity to trial product(s) or related products
- [24] Have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months
- [25] Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
- [26] Have a history of an active or untreated malignancy, or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years
- [27] Have a history of any other condition (such as known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol
- [28] Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle-cell disease)

Prior/Concomitant Therapy

- [29] Treatment with any glucose lowering agent(s) other than stated in the inclusion criteria # 2 in a period of 2 months prior to Visit 1 and between Visit 1 and Visit 3

- [30] Have been treated with prescription drugs that promote weight loss (e.g., Saxenda (liraglutide 3.0 mg), Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], contrave® [naltrexone/bupropion] or similar other bodyweight loss medications including over-the-counter [OTC] medications [e.g., alli®]) within 3 months prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3)
- [31] Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations) or have received such therapy within 1 month of Visit 1; or between Visits 1 and 3

Prior/Concurrent Clinical Trial Experience

- [32] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- [33] Have participated, within the last 30 days in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed
- [34] Have previously completed or withdrawn from this study or any other study investigating tirzepatide

Other Exclusions

- [35] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
- [36] Are Lilly employees
- [37] Are unwilling or unable to comply with the use of a paper diary to directly record data from the subject